Remarks/Arguments

By the present amendment, applicants have cancelled Claims 1-34 and added new Claims 35-54. Therefore the claims remaining for consideration by the Examiner are Claims 35-54.

Applicants provide the following claim chart establishing support for each of the new Claims 35-54.

Claim	Support
35	Cancelled Claims 1, 2, 6, 7, and 19.
36	Cancelled Claim 27.
37	Cancelled Claim 27.
38	Cancelled Claims 24 and 25.
39	Cancelled Claim 25.
40	Cancelled Claim 25.
41	Specification pg. 6, line 12, and pg. 5, line 11.
42	Cancelled Claims 24 and 25.
43	Cancelled Claim 5.
44	Cancelled Claim 3.
45	Cancelled Claim 8.
46	Specification pg. 7, lines 1-3.
47	Specification pg. 7, line 2.
48	Cancelled Claims 22.
49	Cancelled Claim 22.
50	Cancelled Claims 1, 2, 6, 7, 19, and 28.
51	Cancelled Claim 29.
52	Cancelled Claim 1, 2, 6, 7, 19, and 31.
53	Cancelled Claim 32.
54	Cancelled Claim 33.

The Examiner noted that according to 37 CFR 1.77(b), the specification of a utility application should include section headings.

In response, applicants have submitted herewith a substitute specification with the addition of headings. Applicants note that the paragraph under the section entitled, "BRIEF DESCRIPTION OF THE DRAWINGS" was originally located immediately before the examples.

The Examiner noted that the application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b).

In response, applicants have included an abstract on a separate sheet. Applicants' abstract corresponds to applicants' new Example 35.

The Examiner noted that the use of the trademark "Pluronic F-68" in the application should be capitalized wherever it appears and be accompanied by the generic terminology.

In response, applicants have capitalized "PLURONIC" throughout the application wherever it appears. Regarding the generic terminology of the term "Pluronic", applicants note that the term first appears in applicants' specification, on page 3, lines 9-10, wherein "Pluronic" is referred to as a "polyoxyethylene-polyoxypropylene block copolymer". In addition, applicants direct the Examiner's attention to the Handbook of Pharmaceutical Excipients , published by the American Pharmaceutical Association (1986), page 207, wherein poloxamer 188 and Pluronic F-68 are shown to be synonyms for a poly(oxyethylene), poly(oxypropylene) block copolymer. A copy of the relevant sections of the Handbook of Pharmaceutical Excipients is included herewith. Applicants have replaced the term "poloxamer" and "Pluronic" in the claims with poly(oxyethylene)-poly(oxypropylene) block copolymer.

The Examiner has rejected Claims 6-10, 19-21, 23-34 under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend on another multiple dependent claim.

Applicants have canceled Claims 6-10, 19-21, 23-34.

The Examiner has rejected Claims 1-34 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants have canceled Claims 1-34 and added new Claims 35-54.

The Examiner has rejected Claims 3-34 under 35 U.S.C. 112, second paragraph, as being indefinite in that they fail to point out what is included or excluded by the claim language and introduced by frequent use of the relative terms "optionally", "preferably", "more preferably" and "even more preferably".

In response applicants have canceled Claims 3-34, and added new Claims 35-54. Applicants note that the new claims are not omnibus claims. In addition, applicants' new claims do not contain trademark/trade names.

The Examiner has rejected Claims 1-15, 17-30 under 35 U.S.C. 102(b) as being anticipated by WO 94/03198 ('198).

As stated on page 6, lines 15-17, of WO '198, the growth hormone formulation has a pH of from about 4 to 8, more preferably about 5.5 to about 7, most advantageously 6.0. The only pH of the formulations described in the examples of WO '198 is a pH of 6.0.

The pH of applicants' liquid human growth hormone formulation, as claimed, is from 6.15 to 6.5. Applicants unexpectedly determined that this pH range of applicants' formulation avoids the formation of crystals, as well as degradation and/or aggregation of the protein, during storage. WO '198 determines instability from the degradation and/or aggregation of the protein. WO '198 does not recognize the formation of crystals as a stability issue.

Applicants have unexpectedly determined that crystallization occurs upon storage inside or outside of a refrigerator, as stated in applicants' specification on page 5, lines 9-12. While crystallization may be reversible by agitating (shaking) the crystallized solution, this is extremely inconvenient for a patient. Moreover, since crystallization may not be detectable by the patient, and agitation prior to administration may not be performed, the dosage of human growth hormone will be less than the required amount for the patient.

It is further noted that applicants' formulation consists essentially of growth hormone in isotonic phosphate buffered solution, a preservative and a non-ionic surfactant. WO '198, on page 6, lines 1-4, provides a list of buffers which includes "phosphate" among many others. However, the actual formulations prepared in the examples of WO '198 use a citrate buffer.

Since WO '198 does not teach a formulation containing a phosphate buffer wherein the formulation has a pH of 6.15 to 6.5, as claimed by applicants, WO '198 clearly does not anticipate applicants' claims, as amended.

The Examiner has rejected Claims 1-4, 7, 8, 11-15, 17, 18-20, 21, 23-27 under 35 U.S.C. 102(b) as being anticipated by WO 97/07816 ('816).

WO '816 relates to insulin-like growth factor. In addition, WO '816 does not teach or suggest using a surfactant in the formulations containing insulin-like growth factor or any other protein.

In contrast, applicants' claims are directed to human growth hormone. In addition, applicants' formulation, as claimed, includes a nonionic surfactant.

Thus, WO '816 clearly does not anticipate or render obvious applicants' claims, as amended.

The Examiner has rejected Claims 1-7, 9-15, 17, 19, 20, 23-30 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,096,885 ('885). In the alternative, the Examiner has rejected Claims 16 and 22 under 35 U.S.C. 103(a) as being unpatentable over US '885.

U.S. '885 describes a growth hormone formulation containing glycine, mannitol, buffer, and optionally a nonionic surfactant.

In contrast, applicants claims are directed to a formulation containing the term "consisting essentially of" and do not include glycine. In addition, the pH of applicants' liquid human growth hormone formulation, as claimed, is from 6.15 to 6.5. Thus, applicants' pH range as claimed is significantly different than a pH of 7.4 which was used for all of the samples in U.S. '885, as stated in column 5, lines 57-58.

Thus, U.S. '885 clearly does not anticipate or render obvious applicants' claims, as amended.

The Examiner has rejected Claims 1-6, 9-11, 14, 15, 17, 19-21, 23-30 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,126,324 ('324). In the alternative, the Examiner has rejected Claims 16 and 22 under 35 U.S.C. 103(a) as being unpatentable over U.S. '324.

A formulation is described in U.S. '324, in column 10, lines 15-17. The formulation contains insulin-like growth factor, growth hormone, mannitol, glycine, and phosphate, and has a pH of 7.4. U.S. '324 continues, in column 10, lines 17-20, to state that if this formulation is to be stored, it is formulated in a buffer at a pH of about 6, such as citrate, and a surfactant.

In the Example section of U.S. '324, in column 11, lines 19-31, two formulations are described. The first formulation contains growth hormone, mannitol, and phosphate, and has a pH of 7.8. The second formulation contains growth hormone, mannitol, glycine, and phosphate, and has a pH of 7.4.

In contrast, applicants claims require a preservative, such as benzyl alcohol. U.S. '324 describes a long list of additional materials to use in the formulations, in column 9, lines 49-66, but fails to mention preservatives which are required in applicants' claims.

In addition, while U.S. '324 suggests a citrate buffer at a pH of 6, and a phosphate buffer at pH of 7.8, applicants' claims require a phosphate buffer at a pH from 6.15 to 6.5, which range is not taught by U.S. '324. As noted above, applicants unexpectedly determined that this pH range along with specific other ingredients in applicants' formulation, as claimed, avoids the formation of crystals during storage.

Thus, U.S. '324 clearly does not anticipate or render obvious applicants' claims, as amended.

The Examiner has rejected Claims 1-4, 7, 8, 11-15, 17, 18-20, 21, 23-30 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,567,677 ('677). In the alternative, the Examiner has rejected Claims 16, 22 under 35 U.S.C. 103(a) as being unpatentable over U.S. '677.

U.S. '677 states, in column 3, lines 6-9, that "we have now found that solutions containing growth hormone in which citrate has been chosen as a buffer substance are more

stable than those in which phosphate is the buffer". In the Examples of U.S. '677, twelve formulations were prepared. All of the comparative formulations which were prepared with a phosphate buffer also contained glycine.

In contrast, applicants' claims require a phosphate buffer. In addition, applicants claims are limited by the term "consisting essentially of" and do not include glycine. Applicants' claims are further distinguished over U.S. '677 by the required presence of a nonionic surfactant. U.S. '677 does not teach or suggest using a surfactant in the formulations.

Thus, U.S. '677 clearly does not anticipate or render obvious applicants' claims, as amended. In fact, U.S. '677 teaches away from applicants' formulations by requiring a citrate buffer.

The Examiner has rejected Claims 1-6, 9, 11, 14, 15, 17, 19-21, 23-27 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,610,134 ('134). In the alternative, the Examiner has rejected Claims 10, 16, 22 under 35 U.S.C. 103(a) as being unpatentable over U.S. '134.

A formulation is described in U.S. '134, in column 13, lines 6-9. The formulation contains insulin-like growth factor, growth hormone, mannitol, glycine, and phosphate, and has a pH of 7.4. U.S. '134 continues, in column 13, lines 9-12, to state that if this formulation is to be stored, it is formulated in a buffer at a pH of about 6, such as citrate, and a surfactant.

In the Example section of U.S. '134, in column 14, lines 49-53, a formulation is described which contains growth hormone, insulin-like growth factor, sodium acetate buffer, phenol, sodium chloride, and benzyl alcohol, and has a pH of 5.4.

In contrast, applicants' claims are directed to a formulation "consisting essentially of" and do not include either insulin-like growth factor, glycine, phenol, or sodium acetate buffer which are used in the formulations of U.S. 134. In addition, the pH of applicants' liquid human growth hormone formulation, as claimed, is from 6.15 to 6.5. Thus, applicants' pH range as claimed is significantly different than a pH of 7.4 or 5.4, as used in the formulations of U.S. '134.

Thus, U.S. '134 clearly does not anticipate or render obvious applicants' claims, as amended.

The Examiner has rejected Claim 16 under 35 U.S.C. 103(a) as being unpatentable over WO '198.

WO '198, on page 6, lines 15-17, states that the growth hormone formulation has a pH of from about 4 to 8, more preferably about 5.5 to about 7, most advantageously 6.0. The only pH of the formulations described in the examples of WO '198 is a pH of 6.0.

In contrast, the pH of applicants' liquid human growth hormone formulation, as claimed, is from 6.15 to 6.5. Applicants unexpectedly determined that this pH range of applicants' formulation avoids the formation of crystals, as well as degradation and/or aggregation of the

protein, during storage. WO '198 determines instability from the degradation and/or aggregation of the protein. WO '198 does not recognize the formation of crystals as a stability issue.

It is further noted that applicants' formulation consists essentially of growth hormone in isotonic phosphate buffered solution, a preservative and a non-ionic surfactant. WO '198, on page 6, lines 1-4, provides a list of buffers which includes "phosphate" among many others. However, the examples of WO '198 use a citrate buffer. In addition, WO '198 states on page 7, lines 12-14, that a succinate or acetate buffer could be employed instead of a citrate buffer. It is further noted that WO '198 prepared comparison examples using a phosphate buffer, sodium phosphate, in a lyophilized formulation, as stated on page 8, lines 33-39. The comparison examples decolorized after only 30 minutes of shaking, as stated on page 11, lines 20-23.

Thus, WO '198 clearly does not teach applicants' human growth hormone formulation containing a phosphate buffer wherein the formulation has a pH of 6.15 to 6.5, as claimed by applicants.

The Examiner has rejected Claims 31-34 under 35 U.S.C. 103(a) as being unpatentable over WO '198 in view of U.S. Patent No. 5,334,162 ('162).

As noted above, WO '198 does not teach applicants' human growth hormone formulation containing a phosphate buffer wherein the formulation has a pH of 6.15 to 6.5, as claimed by applicants.

U.S. '162 describes a cartridge assembly for a lyophilized drug such as human growth hormone. U.S. '162 does not teach or suggest formulations containing human growth hormone.

In contrast, applicants claims are directed to a formulation "consisting essentially of" and require the formulation to be liquid not lyophilized.

Thus, the combination of WO '198 and U.S. '162 does not place one skilled in the art in possession of applicants' human growth hormone formulation, as claimed.

The Examiner has rejected Claims 28-34 under 35 U.S.C. 103(a) as being unpatentable over WO '816 in view of US '162.

As noted above, WO '816 relates to insulin-like growth factor which is a protein unrelated to human growth hormone. In addition, WO '816 does not teach or suggest using a surfactant in the formulations. None of the examples in WO '816 contain a surfactant.

In contrast, applicants' claims are directed to human growth hormone. In addition, applicants' formulation, as claimed, includes a nonionic surfactant.

Furthermore, WO '816 does not specify a pH range for the formulation, other than to use a pH of 5.9 in the examples. In contrast, the pH of applicants' liquid human growth hormone formulation, as claimed, is from 6.15 to 6.5.

U.S. '162 describes a cartridge assembly for a lyophilized drug such as human growth hormone. U.S. '162 does not teach or suggest formulations containing human growth hormone.

Thus, combining WO '816 and U.S. '162 does not place one skilled in the art in possession of applicants' human growth hormone formulation, as claimed.

The Examiner has rejected Claims 31-34 under 35 U.S.C. 103(a) as being unpatentable over US '885 in view of US '162.

As noted above, U.S. '885 describes a growth hormone formulation containing glycine, mannitol, buffer, and optionally a nonionic surfactant.

In contrast, applicants claims are directed to a formulation containing the transition language "consisting essentially of" and do not include glycine.

U.S. '162 describes a cartridge assembly for a lyophilized drug such as human growth hormone. U.S. '162 does not teach or suggest formulations containing human growth hormone.

Thus, combining U.S. '885 and U.S. '162 does not place one skilled in the art in possession of applicants' human growth hormone formulation, as claimed.

The Examiner has rejected Claims 31-34 under 35 U.S.C.103(a) as being unpatentable over U.S. '324 in view of US '162.

As noted above, U.S. '324 does not teach or suggest a human growth hormone formulation containing a preservative as required by applicants' claims. While U.S. '324 describes a long list of additional materials to use in the formulations, in column 9, lines 49-66, it fails to mention preservatives.

U.S. '162 describes a cartridge assembly for a lyophilized drug such as human growth hormone. U.S. '162 does not teach or suggest formulations containing human growth hormone.

Thus, combining U.S. '324 and U.S. '162 does not place one skilled in the art in possession of applicants' human growth hormone formulation, as claimed.

The Examiner has rejected Claims 31-34 under 35 U.S.C. 103(a) as being unpatentable over US '677 in view of US '162.

As noted above, U.S. '677 states, in column 3, lines 6-9, that "we have now found that solutions containing growth hormone in which citrate has been chosen as a buffer substance are more stable than those in which phosphate is the buffer". In the Examples of U.S. '677, twelve formulations were prepared. All of the formulations which were prepared with a phosphate buffer also contained glycine. Only one of the formulations did not contain glycine, but was prepared with sodium citrate buffer.

In contrast, applicants' claims require a phosphate buffer. In addition, applicants claims are limited by the term "consisting essentially of" and do not include glycine. Applicants' claims are further distinguished over U.S. '677 by the required presence of a nonionic surfactant. U.S. '677 does not teach or suggest using a surfactant in the formulations.

U.S. '162 describes a cartridge assembly for a lyophilized drug such as human growth hormone. U.S. '162 does not teach or suggest formulations containing human growth hormone.

Thus, combining U.S. '677 and U.S. '162 does not place one skilled in the art in possession of applicants' human growth hormone formulation, as claimed.

The Examiner has rejected Claims 28-34 under 35 U.S.C. 103(a) as being unpatentable over US '134 in view of US '162.

As noted above, U.S. '134 describes only two formulations. The first formulation contains insulin-like growth factor, growth hormone, mannitol, glycine, and phosphate, and has a pH of 7.4. The second formulation contains growth hormone, insulin-like growth factor, sodium acetate buffer, phenol, sodium chloride, and benzyl alcohol, and has a pH of 5.4.

In contrast, applicants' claims use the transition language "consisting essentially of" and do not include either insulin-like growth factor, glycine, phenol, or sodium acetate buffer which are used in the formulations of U.S. 134. In addition, the pH of applicants' liquid human growth hormone formulation, as claimed, is from 6.15 to 6.5. Thus, applicants' pH range as claimed is significantly different than a pH of 7.4 or 5.4, as used in the formulations of U.S. '134.

U.S. '162 describes a cartridge assembly for a lyophilized drug such as human growth hormone. U.S. '162 does not teach or suggest formulations containing human growth hormone.

Thus, combining U.S. '677 and U.S. '162 does not place one skilled in the art in possession of applicants' human growth hormone formulation, as claimed.

None of the references recognize the formation of crystals in a liquid human growth hormone formulation as a serious problem for patients. Moreover, none of the references, evaluated alone or in combination, suggest applicants' liquid human growth hormone formulation, as claimed, as a solution to prevent the formation of crystals.

Respectfully submitted,

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Date: December 6, 2004